REMARKS

Support for Amendments

As noted above, Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are currently pending in the application. In order to advance prosecution, Applicants have amended claims 3, 16, 17, 21, 23, 24, 30, 33, and 37, and have cancelled claims 38-40. Claims 1, 2, 4-15, 18-20, 22, 25-29, 31, 32, and 34-36 were previously withdrawn. Applicants reserve the right to pursue the subject matter of the previously-filed, withdrawn, or cancelled claims in this or another appropriate patent application.

The amendments to the claims are made without prejudice, do not constitute amendments to overcome any asserted prior art rejections under U.S.C. § 102 or 103, and are fully supported by the specification as filed and the cited priority documents. For example, the amendment to claim 37 includes the limitations of canceled claims 38 and 39, and further support can be found in claims 15, 18, and 19 of the application as originally filed. Further support for the amendments to claims 3, 16, 17, 21, 23, 24, 30, 33, and 37, specifically, use of the term "siRNA" rather than "siNA", can be found in the definition of the term "siNA", which includes the term "siRNA", see for example page 70, lines 27-28. These amendments add no new matter and Applicants respectfully request their entry.

THE OFFICE ACTION

I. Priority

The Office Action asserts that the present invention is not entitled to priority to the cited priority documents, including provisional application 60/363,124, filed March 11, 2002. The Office Action alleges that the term "siNA" cannot be found in the 60/363,124 provisional application. The Applicant respectfully disagrees with this assertion because the term "siNA" as defined by the specification as filed includes the term "siRNA", which refers to short interfering RNA. The definition also contemplates siNA or siRNA that is completely modified. Completely modified siRNA molecules are described in the 60/363,124 provisional application

as well (see for example pages 5-14, wherein one or more, including all nucleotides present in a given siRNA are chemically modified with modifications as represented both by chemical formulae and also nomenclature as is recognized in the art). However, in the interest of advancing prosecution, claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 have been amended to replace the term "siNA" with the term "siRNA".

The Office Action also asserts that the present invention is not entitled to priority because the 60/363,124 provisional application does not "describe the short interfering nucleic acid sequences themselves that are complementary to human synuclein-1" and that "[t]he description of the individual sequences themselves is critical, since the pre- and post- filing art clearly indicates that, in general, significant variability exists with regard to the functionality of individual siRNAs targeting the same gene" (see Office Action at page 5). The Office Action cites Harborth *et al.*, 2001, *J. Cell Science*, 114:4557-4565, which states "Currently we do not know whether the occasional ineffectiveness of a siRNA duplex arises from secondary structure of the mRNA, protection of the mRNA by a binding protein, or an as yet unidentified feature in the sequence of the duplex". The key here is the word "occasional ineffectiveness". Compared to previous nucleic acid technologies, siRNAs are robust, and are currently recognized to effectively inhibit the expression of any gene target.

The fact that some siRNAs do not have activity is not material to a 35 U.S.C. §112 analysis for the purpose of establishing priority for the presently claimed invention. It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005). Because the 60/363,124 provisional application teaches how to design, synthesize, test, and administer siRNA molecules targeting human SNCA RNA, specifically SEQ ID NO:311 (see page 305, referring to NM_000345), the teachings of the provisional application would allow one of skill in the art at the time to recognize that the Applicant was in possession of the claimed invention. Furthermore, the 60/363,124 provisional application teaches the structure function relationship between siRNAs and their targets, *i.e.*, complementarity of the antisense strand to the target RNA, complementarity between the sense and antisense strands, the requisite length of

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the siRNA sense and antisense strands, chemical modifications that maintain RNAi activity (contrary to reports from the prior art at the time, including the Elbashir and Parrish references cited by the Office Action) and the specific sequence of the target which allows the corresponding design of active siRNA molecules. In addition, the 60/363,124 provisional application provides representative data of numerous siRNA molecules, including chemically modified siRNA molecules as presently claimed, that effectively inhibit the expression of a representative number of examples of different gene targets. All of these parameters are taught by the 60/363,124 provisional application and would lead one of skill in the art at the time to recognize that the Applicant was in possession of the claimed invention at the time of the provisional filing.

Under 35 U.S.C. § 112, first paragraph, all that is required to satisfy the written description requirement is that the specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); M.P.E.P § 2163(I). Possession is shown "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *See,* M.P.E.P. § 2163.02 (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir.1997)). Applicant has fulfilled these requirements with respect to the instantly claimed invention in the 60/363,124 provisional application by providing such descriptive means in the way of specific embodiments, figures, and examples that detail the structure of siRNA molecules. For example, claim 37 has specific support in the 60/363,124 application for "a chemically synthesized siRNA molecule" at page 3, lines 15-17; page 32, lines 11-12; page 35, lines 29-30; and page 60, line 20; "having complementarity between a first strand and a second strand" at page 3, lines 7-9; page 12, lines 4-7; page 19, lines 11-14; page 21, lines 3-6; and page 25, lines 17-29; "one strand having 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311" at page 18, lines 1-5; page 60, lines 18-21; and page 305, referring to GenBank Accession number NM_000345; and "one or more pyrimidine nucleotides present in the first strand or second strand of the siRNA molecule is a 2'-deoxy-2'-

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fluoro pyrimidine nucleotide" at page 10, lines 11-14, 25-27; page 11, lines 6-9; and pages 75-76 (SEQ ID NOS:333, 336, 339, and 342-348).

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. *See*, M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; and (5) the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient. *Id*; *see, Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Specifically, the written description requirement can be met by a functional description of claimed materials, if it is coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002). Contrary to the Office's assertions, the application as filed describes the requisite identifying characteristics of the claimed invention by providing an adequate functional description of the claimed invention by describing how to design, synthesize and test siRNAs that target human SCNA having SEQ ID NO:311. The specification also describes both structural and functional aspects of the claimed invention by teaching the specific structures of representative siRNA molecules as are presently claimed targeting various nucleic acid targets. The priority application teaches how to design a siRNA molecule against any target in Example 5, beginning on page 57, line 24. The priority application also shows representative data which demonstrates that chemically modified siRNA molecules have the same activity as unmodified siRNA molecules as is shown in Figures 4-10, with corresponding descriptions on pages 30 and 55-57. Using the teachings of the 60/363,124 provisional application, Applicant has provided numerous examples of the claimed invention in the instant application US 10/698,311. All of these teachings provide specific written description of the claimed invention.

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Furthermore, merely in the interest of advancing prosecution, Claim 1 has been amended to include both functional and structural limitations to provide clarification and particularity to the subject matter of the invention, as presently claimed. Specifically, claim 37 has been amended to recite a chemically synthesized double stranded short interfering RNA (siRNA) molecule consisting essentially of a first nucleic acid strand and a second nucleic acid strand, wherein the first strand has complementarity to the second strand; the second strand has 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311; and one or more pyrimidine nucleotides present in the first strand or second strand of the siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. In contrast to the Office's assertions, Applicants have adequately described the distinguishing identifying structural and functional characteristics of the claimed subject matter and has provided several examples of the claimed siRNA nucleic acid molecules, all of which demonstrate that the Applicant had possession of the claimed invention at the time of filing. Therefore, the Applicant respectfully requests entry of priority to the 60/363,124 provisional application for the instantly claimed invention.

II. Rejection of Claims under 35 U.S.C. § 112

Claim 27 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 has been canceled, thus rendering the rejection moot. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 rejection.

III. Rejection of Claims under 35 U.S.C. § 103

Claims 3, 21, 23, 27, 30, 33 and 37-40 stand rejected as allegedly obvious over Tuschl *et al.* (US 2004/0259247), Driscoll *et al.* (WO 01/49844) and GenBank Accession No. D31839. Claims 27, and 38-40 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 3, 21, 23, 30, 33, and 37.

In the interest of advancing prosecution, claim 37 has been amended to recite a chemically synthesized double stranded short interfering RNA (siRNA) molecule consisting

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essentially of a first nucleic acid strand and a second nucleic acid strand, wherein the first strand has complementarity to the second strand; the second strand has 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311; and one or more pyrimidine nucleotides present in the first strand or second strand of the siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

Here, the knowledge of one of ordinary skill prevented the inventions claimed in the instant application from being realized. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g.*,

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Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Tuschl describes double stranded RNA molecules having 2-4 deoxynucleotides at the 3'-ends of double stranded RNA molecules. Driscoll teach inverted repeat constructs that express long double stranded RNAs complementary to GenBank Accession No. D31839. None of these cited references either individually or in combination make obvious the claimed invention. The Office Action states that one of skill in the art would be motivated by the teachings of Driscoll to inhibit the expression of the D31839 sequence using siRNA molecules as taught by Tuschl, and that "it would have been obvious to one of ordinary skill in the art to incorporate nucleotide modifications as taught by Tuschl et al. into said siRNA molecules" (Office Action page 16). The Tuschl application was filed on July 26, 2004, which is after the date of the instant invention, but claims priority to WO 02/44321. As described below, WO 02/44321 teaches away from the presently claimed invention.

Tuschl (WO 02/44321) attempted to apply chemical modifications to siRNA but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of page 46 of Tuschl (WO 02/44321) describes 2'-deoxy and 2'-O-methyl modified siRNA duplexes and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional

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> ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 14 of Tuschl (WO 02/44321) clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where 2'-O-methyl substitutions were used, this modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on pages 49-50 of WO 02/44321:

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Based on the teachings of "[t]he siRNA Users Guide" from Tuschl, for example, one of skill in the art would not be motivated to make any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not be motivated to pursue the presently claimed invention. This is evident from the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Tuschl and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; Holen *et al.,* 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references demonstrate that Tuschl taught away from the presently claimed invention

The Applicant has shown that 2'-deoxy-2'-fluoro modifications, and importantly, modification of internal base-paired nucleotide positions, are well tolerated in siRNA molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize siRNA molecules as presently claimed to successfully target gene expression. For example, in the 60/363,124 provisional priority application and in co-pending application USSN 10/444,853, published as US2004-0192626, applicant has designed, synthesized, and tested 2'-deoxy-2'-

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fluoro pyrimidine modified double stranded nucleic acid molecules having potent activity directed against various targets, (*see, e.g.,* Figure 7 of the 60/363,124 provisional priority application, and US2004-0192626 Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-15). This co-pending application, along with many others, demonstrate that application of 2'-deoxy-2'-fluoro pyrimidine modifications to double stranded nucleic acid structures are well tolerated for maintaining potent RNAi activity against target nucleic acid sequences. Therefore, a person skilled in the art would not have been motivated to follow the teachings of Tuschl to make and use the double stranded nucleic acid molecules of the present invention to target human SNCA.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made (see discussion of priority above). *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000). The Office Action asserts that "one would have a reasonable expectation of success given that Tuschl provide detailed guidelines and rules for generating siRNA to any known gene" (See Office Action page 16). Applicants provide the same information, *i.e.,* how to generate siRNA to any know gene. However, as opposed to Tuschl, who fail to teach against modification of siRNA beyond 3'-terminal 2'-deoxynucleotide substitution, Applicant teaches how to design siRNAs that are more extensively modified, including modification of the sense strand, the antisense strand, or both sense and antisense strands of the siRNA with one or more pyrimidine nucleotides modified with 2'-deoxy-2'-fluoro nucleotides which are tolerated in short double stranded nucleic acid

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molecules as presently claimed and effective in down-regulating gene expression as is described in the Applicant's own work.

For the reasons set forth above, Tuschl *et al.* (US 2004/0259247), Driscoll *et al.* (WO 01/49844) and GenBank Accession No. D31839 do not teach or suggest making a chemically synthesized double stranded short interfering RNA (siRNA) molecule consisting essentially of a first nucleic acid strand and a second nucleic acid strand, wherein the first strand has complementarity to the second strand; the second strand has 18-24 nucleotides complementary to a human synuclein-1 (SNCA) RNA comprising SEQ ID NO:311; and one or more pyrimidine nucleotides present in the first strand or second strand of the siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide with a reasonable expectation of success. Therefore, because there would be no motivation to combine the cited references and because there would be no reasonable expectation of success in such a combination, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

Rejection of Claims 3, 16, 17, 21, 23, 24, 27, 30, 33, and 37-40 Under Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 3, 16, 17, 21, 23, 24, 27, 30, 33, and 37-40 stand as provisionally rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Appl. No. 10/861,060. Claims 27 and 38-40 have been canceled. Therefore, the rejection is moot as applied to these claims.

While not in agreement with the Office Action on this rejection, Applicants, in the interest of efficient prosecution of this application, will consider submitting a terminal disclaimer over U.S. Appl. No. 10/861,060 upon indication of allowable claims in the instant application.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

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Respectfully submitted,

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